Transgender Health
Volume 8, Number 1, 2023
© Mary Ann Liebert, Inc.
DOI: 10.1089/trgh.2021.0023

Open camera or QR reader and scan code to access this article and other resources online.

SHORT REPORT

Transgender and Alagille Syndrome: A Rare Case of a Trans Woman with Alagille Syndrome

Hadas Shefler,[1,2,*,†] Ariel Berl,[2,3,†] and Alon Liran[1,2]

Abstract

Alagille syndrome is a rare autosomal dominant disorder with variable expression. Liver damage, especially cholestatic, is the most common feature of the syndrome.

Transgender patients may suffer from a great distress due to the discrepancy between assigned sex at birth and unaffirmed gender identity.

Gender affirmation treatment options for these patients include hormone therapy (HT) to induce secondary sexual characteristics and various surgical procedures. Estrogen-based hormonal treatments have been linked to an increased risk of liver enzyme elevation and disruption of bilirubin metabolism, especially in those with a genetic susceptibility. The case presented here is the first described Alagille syndrome transgender patient to undergo gender affirmation treatment, including (HT) and vulvo-vaginoplasty surgery.

Keywords: Alagille syndrome; gender affirmation; gender affirming surgery; hormonal therapy; transgender; vulvo-vaginoplasty

Introduction

Transgender patients have a gender identity that is different than that assigned at birth. Some experience distress affecting their daily functioning due to this incongruence, also known as gender dysphoria.[1] Some patients seek medical interventions to better match that of their identity.

Alagille syndrome is a rare autosomal dominant disorder with variable expression and a prevalence of 1:30–100,000.[2–4] The syndrome affects several systems and includes cholestatic liver disease, congenital heart malformations, dysmorphic facies, skeleton abnormalities, and ocular manifestations.[2–5] Liver damage is the most common feature of the syndrome where 15–21% of all patients will suffer from fulminant liver failure necessitating transplantation at different ages.[2,6] Congenital heart anomalies are often present and can be an indicator of early mortality.[6,7]

At presentation to the physician, transgender patients seeking gender affirmation are often treated with hormone therapy (HT) or different surgical procedures or a combination of these according to patient preference.

The HT protocol for trans women generally includes estrogen-based preparations, antiandrogens, and sometimes progesterone to stimulate the development of feminine secondary sex characteristics and induce a feminine appearance that includes breast enlargement, fat redistribution, skin changes, and male pattern baldness.[8–12] Estrogen-based hormonal therapy has been linked to an increased risk of thromboembolic events, coronary and cerebrovascular disease, and liver disease.[10] Medications or supplements composed of estrogens were initially associated with an elevation in liver enzymes, including cholestatic liver damage. Further research and development led to the

[1]Department of Plastic and Reconstructive Surgery, The National Burn Center, Sheba Medical Center, Tel Hashomer, Israel.
[2]Affiliated with the Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel.
[3]Department of Plastic Surgery, Meir Medical Center, Kfar Saba, Israel.
[†]These authors contributed equally to this work.

*Address correspondence to: Hadas Shefler, MD, Department of Plastic and Reconstructive Surgery, The National Burn Center, Sheba Medical Center, Tel Hashomer 52621, Israel, E-mail: hadasmoser@gmail.com

development of products with decreased hepatotoxicity.[13] In those patients who are genetically susceptible, the effects of estrogen on bilirubin metabolism increase the risk of jaundice.

The Endocrine Society, comprised associations from the United States and Europe, and the World Professional Association for Transgender Health have published standards of care regarding the need for evaluation of conditions that warrant special attention before treatment, protocols, and scheduled follow-ups in specialist's office.[10]

Genital gender affirmation surgery (gGAS) can be a part of the process and is recognized as a medical necessity in helping transgender patients with their dysphoria and has been shown to improve many aspects of patients' lives, including physical, social, and mental health.[12,14] Before gGAS for trans feminine patients, testosterone levels are suppressed using different medications. Postoperatively, estrogen supplementation is continued and is usually sufficient to general health. Vulvo-vaginoplasty is the term used to describe the gGAS procedure used to create a neovaginal canal and external female genitalia. The canal can be created by using local skin flaps, skin grafts, or parts of the intestine.[8] The penile inversion technique is the most common method used and is the technique of choice in our institution.[8,15] Attention to the diverse trans subpopulation of patients is required as complex needs can pose medical, ethical, and other dilemmas and necessitate special care. Studies estimate that 0.33–1.6% of the population have trans or nonbinary identities.[16,17]

To our knowledge, no case or study has been published or conducted assessing the risk for liver damage and cardiovascular disease in patients who are genetically susceptible such as Alagille syndrome patients undergoing gender affirmation.

The case presented here is the first described Alagille syndrome trans patient to undergo HT and vulvo-vaginoplasty.

Case Presentation

A 21-year-old trans woman was referred to our institution for gGAS in March 2020.

She was diagnosed with Alagille syndrome in infancy after a liver biopsy was consistent with histological features of the syndrome. Manifestations of the disease included paucity of intrahepatic biliary ducts, pectus carinatum, suspected pulmonary artery stenosis, duplicated renal collecting system, and dysmorphic facial features, including a prominent forehead, pointed chin, and down-slanted palpebra with moderate hypertelorism.

Upon presentation to our department, the patient had already been treated with HT for over 2 years. Her regimen included estradiol and antiandrogen therapy, and she had not experienced any serious adverse events. It is important to note that before initiation of HT, maximal bilirubin levels were 4.8 mg/dL (normal range 0.3–1.2 mg/dL) mostly unconjugated with normal liver function tests (LFTs). The treating endocrinologist conducted a thorough assessment and consulted with specialists worldwide as to whether a patient diagnosed with Alagille syndrome can undergo estrogen supplementation. She was initially started on transdermal estrogen therapy as no current literature was found regarding the risk for adverse effects. Immediately before initiation of therapy, bilirubin levels were 2.6 mg/dL, these elevated to 4.1 mg/dL at first follow-up, and therapy was continued with close follow-ups. Later, the patient was switched to an estrogen-based gel therapy (0.06% estradiol) due to technical inconvenience with the transdermal patch regimen. Antiandrogen therapy was added, initially spironolactone was administered but due to insufficient depression of androgens, the regimen was changed to Zoladex® (goserelin) 3.6 mg once a month with acceptable results. Breasts had enlarged to patient satisfaction, fatty deposits mobilized to thigh region, and libido was slightly lowered. Facial and body hair removal was initiated. When consulted, she did not opt to preserve fertility.

Physical examination upon presentation showed a normal-sized phallus and testis. Up to date laboratory work up was conducted before surgery, hemoglobin was 13 g/dL (12–16), bilirubin 1.75 mg/dL (0.3–1.2), and LFT were within normal limits. A chest X-ray was obtained and was consistent with pectus carinatum deformity without any further abnormalities. An echocardiography was completed to test for any undiagnosed cardiac malformations; mild tricuspid regurgitation was seen with normal ventricular size and function. Consultation with a cardiologist was conducted and an approval to proceed with genital surgery was given. Ultrasonographic imaging of liver was within normal limits, the spleen was slightly enlarged, and kidneys were within normal limits. A gastroenterologist consultation suggested adapting anesthesiology medication to the potential risk of developing cholestatic liver damage.

The vulvo-vaginoplasty was conducted using the penile inversion approach. During the surgical procedure,

increased bleeding was noted, and meticulous inspection to check patency of the rectum and urinary bladder with dye was conducted. No perforation or major bleeding was found. Postoperatively, the patient experienced abdominal distention and pain, and therefor,e a computed tomography scan was obtained and was consistent with the diagnosis of colitis. This is a rare finding, one we are yet to notice in surgeries conducted at our department, since no bowel manipulation was performed throughout surgery or hospital stay. Surgical consultation was obtained with recommendations for future follow-up with a colonoscopy after stabilization of postacute phase. Patient was discharged on postoperative day (POD) 7 after initiating dilation of the neovagina three times daily, voiding spontaneously, and passing stool.

Two weeks postoperatively she was seen at our clinic for a follow-up. The majority of skin incisions were healing, yet the distal part of the neo labia majora seemed slow to heal with dehiscence of the surgical suture line. She was also referred to the emergency room twice (POD 10 and POD 15) due to increased discharge and suspected bleeding. Examination showed that the patient was healing well apart from the area described above and no active bleeding was noticed. Two months postoperatively, the surgical wounds had healed, there was normal passage of stool and urine, neovaginal dilations were conducted as instructed, and satisfactory sexual sensation was reported. Conclusively, patient satisfaction with the procedure was high.

Discussion

This is the first report of a patient diagnosed with Alagille syndrome to undergo gender affirmation. Our patient was successfully treated with HT followed by gGAS with satisfactory results. Regarding the colitis found postoperatively, review of available literature found one case report by Baksh from the United Kingdom of a child diagnosed with Alagille syndrome who developed severe ulcerative pancolitis.[18] To the best of our knowledge, this syndrome is not linked to inflammatory bowel diseases and might be an incidental finding. Our patient was yet to complete a colonoscopy although it was recommended several times and the patient was consulted to the necessity of this test.

According to the literature, one of the most common complications after vulvo-vaginoplasty is wound dehiscence.[15,19] Although in our case there was no complete wound dehiscence, the surgical incisions were slow to heal. We cannot attest as to whether this is secondary to the patient's primary disease or incidental due to lack of available data regarding Alagille syndrome and wound healing.

Although Alagille syndrome is an encountered rare disorder, it is important to raise awareness that patients suffering from gender dysphoria are heterogeneous and have variable clinical backgrounds. This case also demonstrates that patients with syndromes and diseases that might affect multiple organs who at first seem unsuitable candidates for gender affirmation therapy should be assessed individually with a multidisciplinary team to determine if therapy should be initiated. Tailoring a personalized regimen for every patient with available interventions is crucial to patient physical and mental health. Gender dysphoria is not a rare condition and medical professionals must be aware that treatments and surgery for gender affirmation are considered standard interventions for gender-diverse patients.[14,16] This also raises the ethical question of when to deter patients from medically necessary affirmative treatments and surgeries. Do we claim the right to decline a patient who seeks help in those complicated cases of syndromic patients who might have increased susceptibility to adverse effects and serious medical complications? The ethical principles of autonomy, nonmaleficence, and beneficence are all crucial in these challenging cases and must be weighed together when consulting our patients in the aim of providing suitable health care to all patients.

Ethics

Our patient has given her consent for publication of this case.

Author Disclosure Statement

No competing financial interests exist.

Funding Information

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 5th Edition. Arlington, VA: American Psychiatric Association, 2013.
2. Turnpenny P, Ellard S. Alagille syndrome: pathogenesis, diagnosis and management. Eur J Hum Genet. 2012;20:251–257.
3. Danks D, Campbell P, Jack I, et al. Studies of the aetiology of neonatal hepatitis and biliary atresia. Arch Dis Child. 1977;52:360–367.
4. Dalacy J. Alagille syndrome: an overview. Neonatal Netw. 2017;36:343–347.

5. Alagille D, Odièvre M, Gautier M, Dommergues J. Hepatic ductular hypoplasia associated with characteristic facies, vertebral malformations, retarded physical, mental, and sexual development, and cardiac murmur. J Pediatr. 1975;86:63–71.
6. Emerick K, Rand E, Goldmuntz E, et al. Features of Alagille syndrome in 92 patients: frequency and relation to prognosis. Hepatology. 1999;29:822–829.
7. McElhinney D, Krantz I, Bason L, et al. Analysis of cardiovascular phenotype and genotype-phenotype correlation in individuals with a JAG1 mutation and/or Alagille syndrome. Circulation. 2002;106:2567–2574.
8. Narayan S, Morrison T, Dugi DI, et al. Gender confirmation surgery for the endocrinologist. Endocrinol Metab Clin North Am. 2019;48:403–420.
9. van Velzen D, Paldino A, Klaver M, et al. Cardiometabolic effects of testosterone in transmen and estrogen plus cyproterone acetate in transwomen. J Clin Endocrinol Metab. 2019;104:1937–1947.
10. Hembree W, Cohen-Kettenis P, Gooren L, et al. Endocrine treatment of gender-dysphoric/gender-incongruent persons: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2017;102:3869–3903.
11. Radix A. Hormone therapy for transgender adults. Urol Clin North Am. 2019;46:467–473.
12. Coleman E, Bockting W, Botzer M, et al. Standards of care for the health of transsexual, transgender, and gender non-conforming people, version 7. Int J Transgend. 2012;13:165–232.
13. LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda, MD: National Institute of Diabetes and Digestive and Kidney Diseases, 2012. Estrogens and Oral Contraceptives. Updated May 28, 2020. Available at: https://www.ncbi.nlm.nih.gov/books/NBK547852/ Accessed January, 2021.
14. Kuzon Jr W, Sluiter E, Gast K. Exclusion of medically necessary gender-affirming surgery for America's armed services veterans. AMA J Ethics. 2018;20:403–413.
15. Ferrando C. Adverse events associated with gender affirming vaginoplasty surgery. Am J Obs Gynecol. 2020;223:267.e1–267.e6.
16. Safer J, Tangpricha V. Care of transgender persons. N Engl J Med. 2019; 381:2451–2460.
17. Deutsch M. Making it count: improving estimates of the size of transgender and gender nonconforming populations. LGBT Health. 2016;3: 181–185.
18. Baksh G. Alagille syndrome and nonspecific inflammatory bowel disease: a new entity. Gastrointest Endosc. 2002;55:AB263.
19. Levy J, Edwards D, Cutruzzula-Dreher P, et al. Male-to-Female gender reassignment surgery: an institutional analysis of outcomes, short-term complications, and risk factors for 240 patients undergoing penile-inversion vaginoplasty. Urology. 2019;131:228–233.

Cite this article as: Shefler H, Berl A, Liran A (2023) Transgender and Alagille syndrome: a rare case of a trans woman with Alagille syndrome, *Transgender Health* 8:1, 108–111, DOI: 10.1089/trgh.2021.0023.

Abbreviations Used

gGAS = genital gender affirmation surgery
HT = hormone therapy
LFTs = liver function tests
POD = postoperative day